Diabetes Management Update:

Standards, Research & Applications

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Disclosures

Sam Dagogo-Jack, MD

Research Grant Support:
- NIH/NIDDK
- American Diabetes Association
- Novartis Pharmaceuticals

Consultant/Speakers Bureau:
- Eli Lilly, Merck, GlaxoSmithKline, Sanofi-Aventis, Joslin Diabetes Center

Stock ownership:
- None

Diabetes Update

1. Diabetes Control and Complications Trial (DCCT)
   - Epidemiology of Diabetes Interventions and Complications (EDIC)
2. Diabetes Prevention Program (DPP)
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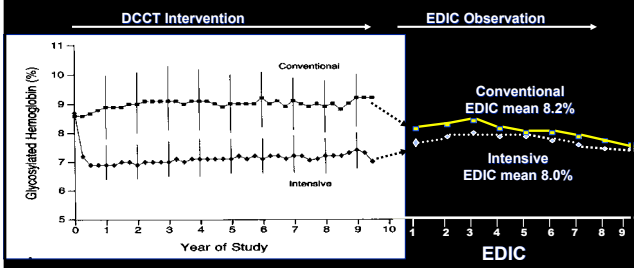
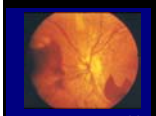
3. Pathobiology of Prediabetes in A Biracial Cohort (POP-ABC)
4. 2009 American Diabetes Association *Clinical Practice Recommendations*

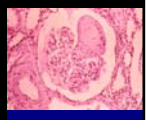
DCCT/EDIC

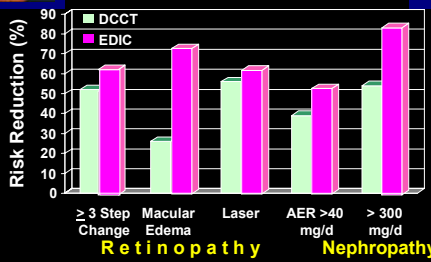


DCCT- Diabetes Control and Complications Trial
EDIC- Epidemiology of Diabetes Interventions and Complications

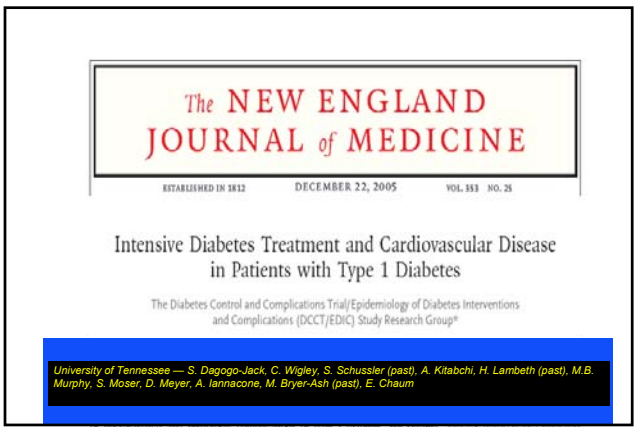
Microvascular Complications



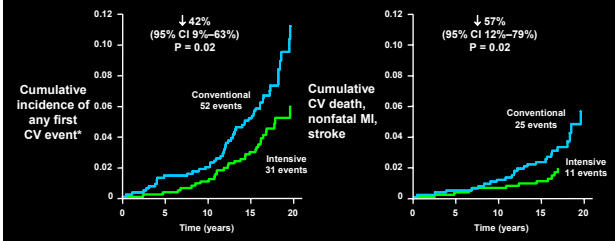




DCCT Research Group. *N Engl J Med*. 2000;342:381-389.



Intensive Glucose Control Reduces CVD Events



* MI, Stroke, CVD death, Silent MI, Angina, Revascularization

DCCT/EDIC Study Research Group. *N Engl J Med.* 2005;353:2643-53.

Explanation of Treatment Group Effect on CVD Events

Treatment Group Effect	Risk Reduction (95% CI)	P	% Group Effect Explained
Baseline Adjusted	47 (17, 66)	0.005	
Adjusted For			
Renal disease	46 (16, 66)	0.005	--
Microalbuminuria	38 (3, 61)	0.03	45
Albuminuria	42 (9, 63)	0.016	29
Mean HbA1c during DCCT	16 (-64, 57)	0.61	97

DCCT/EDIC N Eng J Med 353:2643-2653, 2005

Mechanism(s) of Sustained Benefit in EDIC?

- Metabolic memory or "imprinting"
- Advanced glycosylation end products (AGE)
- Temporal shift in natural history
- Strong rationale for early intervention

CVD Outcomes Trials in Type 2 Diabetes

Trial Design:

CV outcomes following Intensive vs. Standard Rx for T2DM

VADT (Veterans Affairs Diabetes Trial):
- N = 1792, follow-up of 5 to 7 years
- Intensive (HbA1c ≤6.0%) vs. Standard (HbA1c = 8%–9%)

ACCORD (Action to Control Cardiovascular Risk in Diabetes Study:
- N = 10,251, projected median follow-up of 5.6 years
- Intensive (HbA1c ≤6.0%) vs. Standard (HbA1c = 7%-7.9%)

ADVANCE (Action in Diabetes and Vascular Disease):
- N= 11,140 patients with T2DM, median follow-up 5 years
- Intensive (mean 6.5%) vs Standard (mean 7.3%)

ACCORD Group. *NEJM 358:2545, 2008;* ADVANCE Group. NEJM 358:2560, 2008; Duckworth et al. *NEJM 360:129-139, 2009*

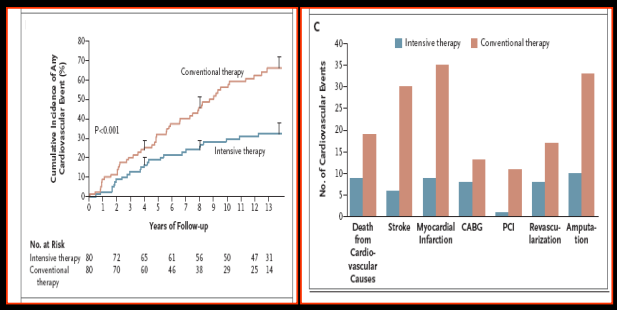
Why are the CVD Results of DCCT/EDIC So Different from the Type 2 Diabetes Studies?

- "Known Knowns"
- Younger age in DCCT
- Shorter duration of T1DM
- No prior CVD, and few risk factors
- Longer follow-up period
- HbA1c level ~7%

- "Known Unknowns"
- Insulin Rx only in DCCT
- Demographic differences
- Rapidity of glycemic decrease
- Magnitude of glycemic decline
- Baseline A1c levels
- Non-glycemic factors

• Glucose is not the major driver of macrovascular disease in type 2 diabetes

Treating the Whole Patient: Steno-2 Composite Cardiovascular Endpoints



Intensive Rx: A1c, BP, LDL, Tg

Gæde P, Lund-Andersen H, Parving H-H, Pedersen O. N Engl J Med 2008;358:580-91.

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DPP Study Interventions

High-risk Prediabetic Subjects*

↓

Randomized

↓

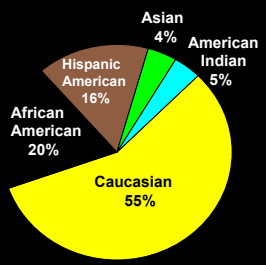
Standard lifestyle recommendations

Intensive Lifestyle (n = 1079)	Metformin (n = 1073)	Placebo (n = 1082)

* IGT plus high risk for T2DM

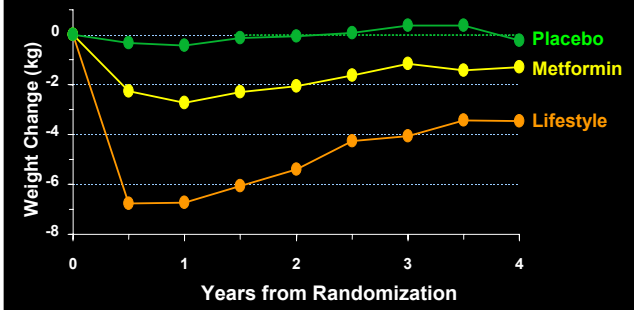
Diabetes Prevention Program
Study Population

Caucasian	1768
African-American	645
Hispanic-American	508
Asian-American & Pacific Islander	142
American Indian	171



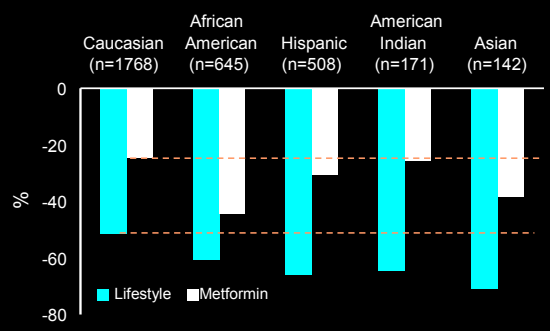
DPP Research Group. NEJM 346:393-403, 2002

Mean Weight Change



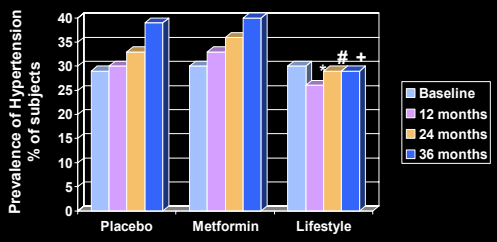
DPP Research Group. NEJM 346:393-403, 2002

Diabetes Risk Reduction by Ethnicity



DPP Research Group. NEJM 346:393-403, 2002

Hypertension



Adapted from DPP Research Group. Diabetes Care 28:888-894, 2005.

Diabetes Prevention: Controlled Clinical Trials

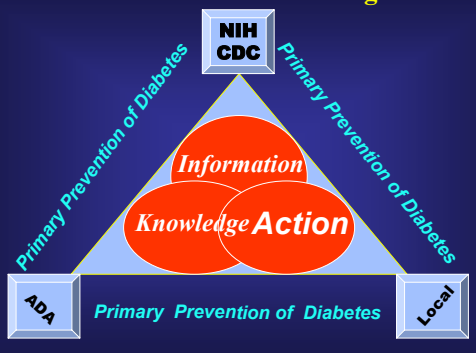
Study (Intervention)	No. of Subjects	Study Population	Risk Reduction
Da Qing (diet ± exercise)	577	Chinese, mean age 45y, BMI 26	31-46% after 6y
STOP-NIDDM (acarbose)	1429	IGT adults, mean age 55 y, mean BMI 31	25% after 3.3 y
Finnish DPS (diet + exercise)	522	IGT adults, mean age 55 y, mean BMI 31	58% after 3.2 y
DPP(Diet + exercise, or Metformin)	3234	IGT adults, mean age 51y, mean BMI 34	Metformin 31%, Lifestyle 58%, after 2.8y
Xendos (orlistat + diet + exercise)	3305	Swedish, BMI > 30, mean age 43yr, 21% with IGT	Entire group 37% , IGT subgroup 45%, after 4y
DREAM (rosiglitazone)	5269	IGT and/or IFG subjects, mean age 54.7y, BMI 30.9	62% after ~ 3y

Edeoga C, Dagogo-Jack S. US Endocrinology, 2009 (in press)

Mechanism(s) of Lifestyle Benefits

- Amelioration of Insulin resistance
- Mobilization of visceral fat
- Modification of adipocytokines
- Epigenetic effects

Translational Challenge



Csdj 2000

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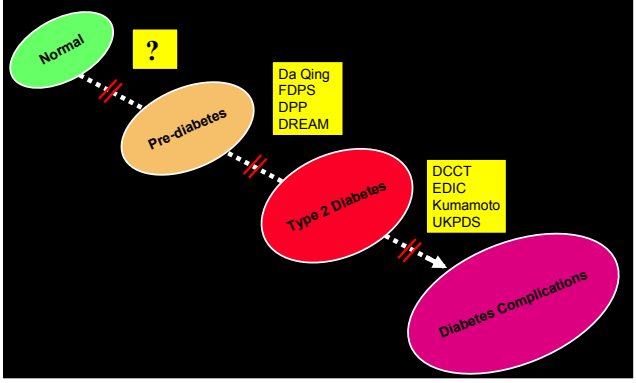
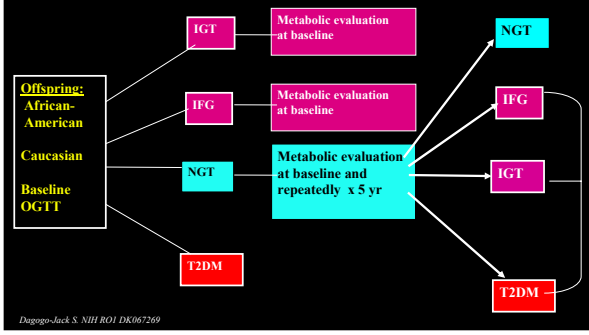
Interrupting the Natural History of Disease



Pathobiology Of Prediabetes in A Bi-racial Cohort (*POP-ABC*)



Dagogo-Jack S. NIH RO1 DK067269

Pathobiology Of Prediabetes in A Bi-racial Cohort
(POP-ABC)

Subjects: Normoglycemic African American and Caucasian offspring of parents with type diabetes

Assessments
- Demographics
- Anthropometry
- Body composition
- Fat distribution
- Caloric intake (FFQ)
- Exercise (MAQ, NHANES)
- Biochemistry
- Insulin secretion (β-cell function)
- Insulin sensitivity (clamp)
- Energy Expenditure
- Inflammatory markers
- Adipocytokines
- Repository-DNA, RNA, Proteome

POP-ABC

WATCHING YOUR HEALTH LIKE A HAWK

901- 448-5299 877-707-1222

http://www.utmem.edu/endocrinology/prediabetes.php

Dagogo-Jack S. NIH RO1 DK067269

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American Diabetes Association Clinical Practice Recommendations Standards of Medical Care in Diabetes 2009

Criteria for the Diagnosis of Diabetes and Pre-Diabetes

NORMAL	IFG or IGT PREDIABETES	DIABETES
FPG < 100 mg/dl	FPG ≥ 100 - 125 mg/dl (IFG)	FPG ≥ 126 mg/dl
2-h PG < 140 mg/dl	2-h PG ≥ 140 < 200 mg/dl (IGT)	2-h PG ≥ 200 mg/dl Random PG ≥ 200 + symptoms

"IFG and IGT have been officially termed pre-diabetes. Both categories of pre-diabetes are risk factors for future diabetes and for cardiovascular disease (CVD)"

Adapted from ADA. Clinical Practice Recommendations-2009. Diabetes Care 32 (suppl 1), S1-S98, 2009

Testing for Pre-diabetes and Diabetes in Asymptomatic Adult Individuals

1. All adults who are overweight (BMI 25 kg/m2*) and have additional risk factors:
   - physical inactivity
   - first-degree relative with diabetes
   - members of a high-risk ethnic population (NA, Latino, AA, Asian, and Pacific Is.)
   - women who delivered a baby weighing >9 lb or were diagnosed with GDM
   - hypertension (140/90 mmHg or on therapy for hypertension)
   - HDL cholesterol level <35 mg/dl and/or a triglyceride level >250 mg/dl
   - women with polycystic ovarian syndrome (PCOS)
   - IGT or IFG on previous testing
   - other conditions associated with insulin resistance (e.g., severe obesity, acanthosis)
   - history of Cardiovascular disease (CVD)

2. In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at age 45 years

3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

Adapted from ADA. Clinical Practice Recommendations-2009. Diabetes Care 32 (suppl 1), S1-S98

Testing for Type 2 Diabetes in Asymptomatic Children

Overweight
BMI >85th percentile for age and sex
Weight for height >85th percentile or
Weight >120% of ideal for height

Plus any two of the following risk factors:

- **FH of type 2 diabetes in first- or second-degree relative**
- **Race/ethnicity (NA, AA, Latino, Asian, Pacific Islander)**
- **Signs of insulin resistance or conditions associated with insulin resistance *(acanthosis nigricans, hypertension, dyslipidemia, PCOS, or small-for-gestational-age birthweight)***
- **Maternal history of diabetes or GDM during the child's gestation**

Age of initiation: age 10 years or at onset of puberty, *whichever is earlier*

Frequency: every 3 years **Test: FPG preferred**

Adapted from ADA. Clinical Practice Recommendations-2009. Diabetes Care 32 (suppl 1), S1-S98

Assessment of Glycemic Control: SMBG and CGM

- SMBG should be carried out: ≥3 times/d for pts using MDII or pump
- SMBG may be useful as a guide to therapy: Patients using fewer insulin injections, noninsulin therapies, or medical nutrition therapy (MNT) and physical activity alone.
- To achieve postprandial glucose targets, postprandial SMBG may be appropriate.
- When prescribing SMBG, ensure patients … ability to use data to adjust therapy.
- CGM in conjunction with intensive insulin regimens can be a useful tool to lower A1C in selected adults (age ≥ 25 years) with type 1 diabetes.
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes.

SMBG- Self-monitoring of blood glucose; CGM-Continuous glucose monitoring

Adapted from ADA. Clinical Practice Recommendations-2009. Diabetes Care 32 (suppl 1), S1-S98, 2009

A1C Recommendations

- Perform the A1C test at least two times a year in patients who are meeting treatment goals (and who have stable glycemic control). (E)
- Perform the A1C test quarterly in patients whose therapy has changed or who are not meeting glycemic goals. (E)
- Use of point-of-care testing for A1C allows for timely decisions on therapy changes, when needed. (E)
- The availability of the A1C result at the time patient is seen (point-of-care testing) has been reported to result in increased intensification of therapy and improvement in glycemic control.*

Adapted from ADA. Clinical Practice Recommendations-2009. Diabetes Care 32 (suppl 1), S1-S98, 2009

* Cagliero E, Levina EV, Nathan DM. *Diabetes Care* 22:1785–1789, 1999

Estimated Average Blood Glucose (eAG)

- The international A1C-Derived Average Glucose (ADAG) trial utilized frequent SMBG and CGM in 507 adults with type 1, type 2, and no diabetes to assess the correlation between A1c and mean blood glucose.
- The ADA and American Association of Clinical Chemists have determined that the correlation ($r = 0.92$) is strong enough to justify reporting both an A1C result and an estimated average glucose (eAG) result when a clinician orders the A1C test.

Adapted from ADA. Clinical Practice Recommendations-2009. Diabetes Care 32 (suppl 1), S1-S98, 2009

Correlation of A1C with Average Glucose

A1C (%)	Mean Plasma Glucose mg/dl	mmol/l
6	126	7.0
7	154	8.6
8	183	10.2
9	212	11.8
10	240	13.4
11	269	14.9
12	298	16.5

http://professional.diabetes.org/eAG

A calculator for converting A1C to eAG, in either mg/dl or mmol/l, is available at http://professional.diabetes.org/eAG.

Glycemic Goals

Glycemic goals in adults

- Lowering A1C to below or around 7% has been shown to reduce microvascular and neuropathic complications of type 1 and type 2 diabetes. Therefore, for microvascular disease prevention, the A1C goal for nonpregnant adults in general is <7%. (A)
- In type 1 and type 2 diabetes, randomized controlled trials of intensive versus standard glycemic control have not shown a significant reduction in CVD outcomes during the randomized portion of the trials.
- Until more evidence becomes available, the general goal of <7% appears reasonable for many adults for macrovascular risk reduction. (B)

Adapted from ADA. Clinical Practice Recommendations-2009. Diabetes Care 32 (suppl 1), S1-S98, 2009

Glycemic Goals

- Subgroup analyses of clinical trials such as the DCCT and UKPDS and the ADVANCE trial suggest a small but incremental benefit in microvascular outcomes with A1C values closer to normal.
- Therefore, for selected individual patients, providers might reasonably suggest even lower A1C goals than the general goal of <7%, if this can be achieved without significant hypoglycemia or other adverse effects of treatment. [Such patients might include those with short duration of diabetes, long life expectancy, and no significant CVD.]
- Less stringent A1C goals than the goal of <7% appropriate for patients with
  - history of severe hypoglycemia, limited life expectancy,
  - advanced microvascular or macrovascular complications,
  - extensive comorbid conditions, and those with longstanding diabetes

  in whom the general goal is difficult to attain despite … effective doses of multiple glucose-lowering agents including insulin. (C)

Adapted from ADA. Clinical Practice Recommendations-2009. Diabetes Care 32 (suppl 1), S1-S98

Summary of Glycemic Recommendations: Non-pregnant Adults

- A1C<7.0%*
  - Preprandial capillary plasma glucose 70–130 mg/dl (3.9–7.2 mmol/l)
  - Peak postprandial capillary plasma glucose <180 mg/dl (<10.0 mmol/l)

Key concepts in setting glycemic goals:

- A1C is the primary target for glycemic control.
- Goals should be individualized based on :
  - duration of diabetes
  - age/life expectancy
  - comorbid conditions
  - known CVD
  - advanced microvascular complications
  - hypoglycemia unawareness
  - individual patient considerations

More or less stringent glycemic goals may be appropriate for individual patients.

Target postprandial BG if A1C goals not met despite reaching preprandial goals

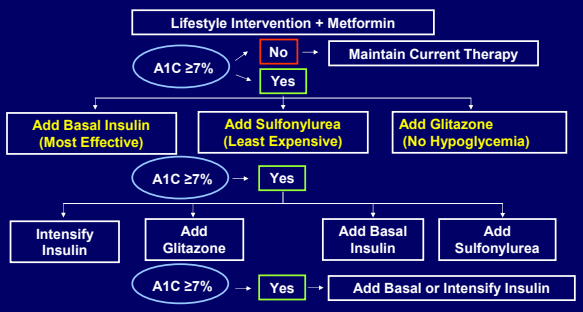
* Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay.
* Postprandial glucose measurements should be made 1–2 h after the beginning of the meal

Diabetes Care 31 (Suppl 1), S1-S98

American Diabetes Association / European Association for the Study of Diabetes

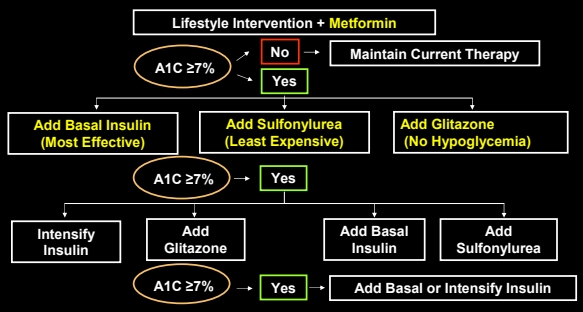
2006 – 2008

ADA / EASD Algorithm : 2006



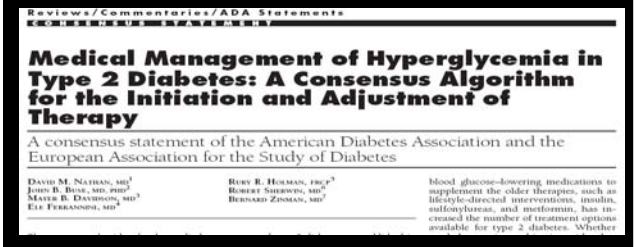
Adapted from Nathan DM, et al. *Diabetes Care.* 2006;29:1963-72.

ADA / EASD Update: January 2008



Nathan et al, DIABETES CARE, VOLUME 31, NUMBER 1, JANUARY 2008

ADA / EASD Algorithm : Update December 2008



Reviews/Commentaries/ADA Statements

CONSENSUS STATEMENT

Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes

DAVID M. NATHAN, MD[1] JOHN B. BUSE, MD, PHD[2] MAYER B. DAVIDSON, MD[3] ELI FERRANNINI, MD[4]

RURY R. HOLMAN, FRCP[5] ROBERT SHERWIN, MD[6] BERNARD ZINMAN, MD[7]

blood glucose–lowering medications to supplement the older therapies, such as lifestyle-directed interventions, insulin, sulfonylureas, and metformin, has increased the number of treatment options available for type 2 diabetes. Whether

"An ADA consensus statement represents the authors' collective analysis, evaluation, and opinion… and does not represent official association opinion."

ADA / EASD Algorithm : December 2008

Tier 1: Well-validated core therapies for type 2 diabetes

- Best established
- Most effective
- Least expensive

a. *Sulfonylureas other than glybenclamide (glyburide) or chlorpropramide.*
b. *Insufficient clinical use to be confident regarding safety.*

Nathan DN et al. *Diabetes Care 31:1-11*, 2008

2009 Statement on the Consensus Panel Algorithm

" The ADA and the European Association for the Study of Diabetes published a consensus statement on the approach to management of hyperglycemia in individuals with type 2 diabetes and recently published an update."

" Highlights of this approach are: intervention at the time of diagnosis with metformin in combination with lifestyle changes and continuing timely augmentation of therapy with additional agents (including early initiation of insulin therapy) as a means of achieving and maintaining recommended levels of glycemic control (i.e., A1C <7% for most patients)."

"The algorithm took into account the evidence for A1C-lowering of the individual interventions, their additive effects, and their expense. The precise drugs used and their exact sequence may not be as important as achieving and maintaining glycemic targets safely."

"Medications not included in the consensus algorithm, owing to less glucose-lowering effectiveness, limited clinical data, and/or relative expense, still may be appropriate choices in individual patients to achieve glycemic goals."

ADA. Standards of Medical Care in Diabetes-2009. Diabetes Care 32 (suppl 1), S23, 2009

Approach to Management of Type 2 Diabetes

M - Monitoring

E - Education

D - Diet

E - Exercise

M - Medications

MNT
- Portion size
- Total calories
- Total/sat. fat
- Cholesterol
- Fiber
- Sodium

Activity
- Duration
- Intensity
- Frequency
- Aerobic
- Resistance
- Strength
- Flexibility

Dagogo-Jack S. In: *Washington Manual of Medical Therapeutics*. 30th ed. 2001.

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Diplomate of the American Board of Endocrinology, Diabetes & Metabolism
UT Bowld Hospital
Memphis, TN 38163
Date:

Name:
Address:_____

Rx:

Walk on your feet for 10 minutes Mon, Wed, Fri or Tues, Thurs, Sat for 1 week, then increase to 20 minutes for another week, and then to 30 minutes on Mon, Wed, Fri or Tues, Thurs, Sat.

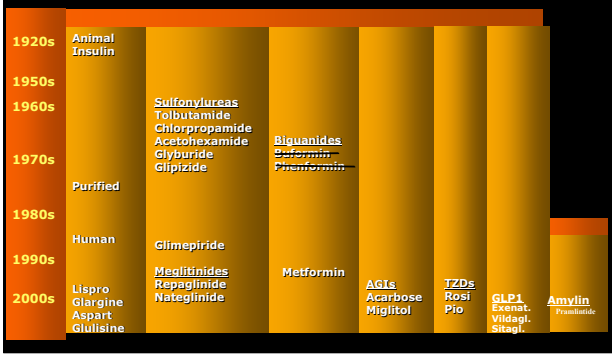
 # Review after 3 months.

Sam Dagogo-Jack, MD

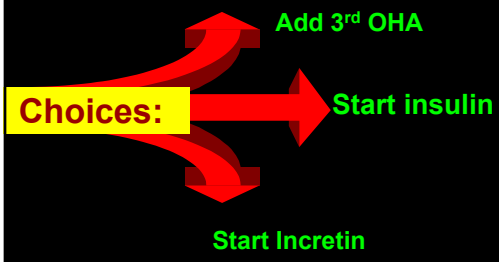
Exercise Rx
- Specific
- Scalable
- Sustainable

Adapted Dagogo-Jack S. *J Natl Med Assoc* 94:549-560, 2002

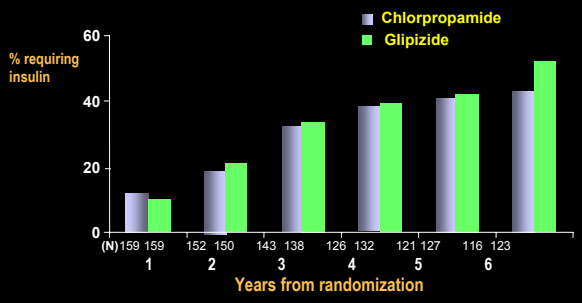
Pharmacologic Treatment of Diabetes Mellitus



What Do You Do When Two Oral Agents Fail to Control Type 2 Diabetes?



UKPDS 57: Percent of Patients Requiring Early Addition of Insulin



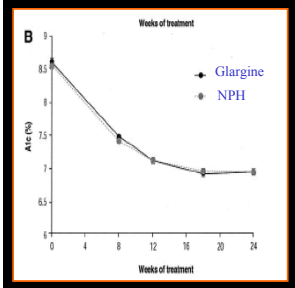
Wright, et al. Diabetes Care. 2002;25:330-336.

Treat-to-Target: Methods

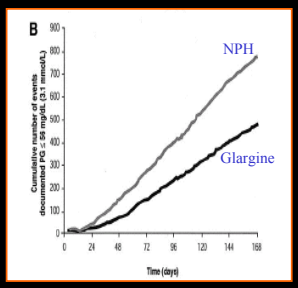
- Multicenter, randomized, parallel-group trial
- Patients: insulin-naïve with type 2 diabetes taking:
  - A sulfonylurea or metformin alone
  - A sulfonylurea + metformin
  - A sulfonylurea or metformin + a glitazone
- Patients treated to FPG ≤100 mg/dL with the addition of once-daily bedtime insulin glargine or NPH
- 10 units hs, increased according to a forced-titration algorithm

Riddle, Rosenstock, Gerich et al. Diabetes Care 26:3080-3086, 2003

HbA1c Level



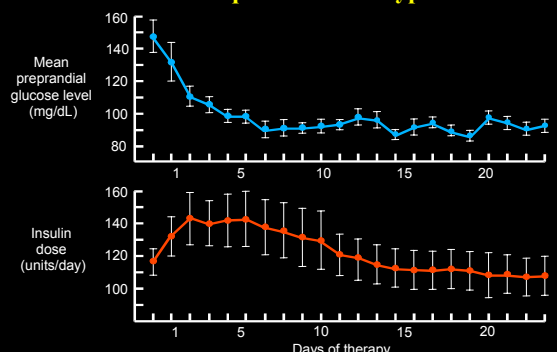
Hypoglycemia



Riddle, Rosenstock, Gerich et al. Diabetes Care 26:3080-3086, 2003

How much insulin?

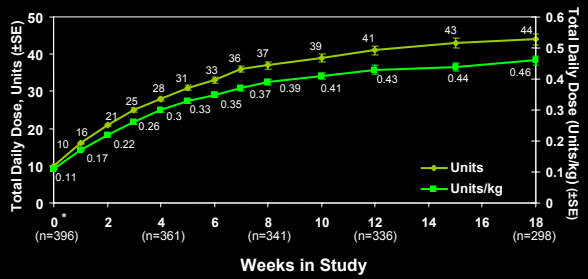
Insulin Requirements in Type 2 Diabetes



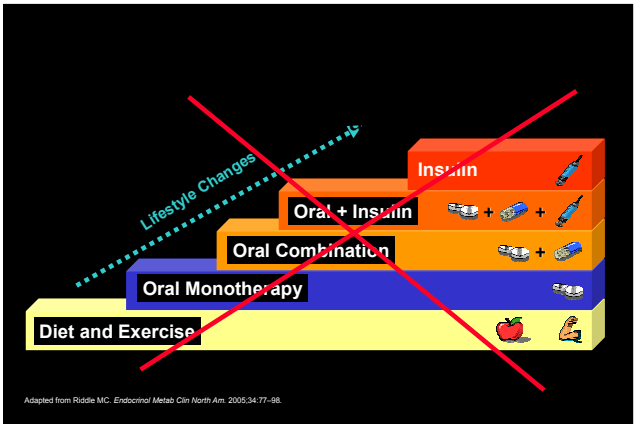
Garvey WT, et al. *Diabetes*. 1985;34:222-234.

Insulin Dosage During Study

(Both treatment groups)



Riddle, Rosenstock, Gerich et al. Diabetes Care 26:3080-3086, 2003



Adapted from Riddle MC. *Endocrinol Metab Clin North Am.* 2005;34:77–98.

Final Thought…

"It is much more important to know what sort of person this disease has than what sort of disease this person has."

– William Osler, MD

Dubos RJ. *Mirage of Health: Utopias, Progress, and Biological Change*. New Brunswick, NJ: Rutgers Univ Press; 1987.